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**DEVELOPMENT OF AN EFFICACIOUS EXERCISE AS A COUNTER MEASURE
OF MUSCLE ATROPHY**

**NASA - AMES RESEARCH CENTER
GRANT #NAG 2-450**

**FINAL TECHNICAL REPORT
4/1/93 - 6/30/95**

**PRINCIPAL INVESTIGATOR - V. REGGIE EDGERTON, PH.D.
CO-INVESTIGATORS:**

**ROLAND R. ROY, PH.D
JOHN A HODGSON, PH.D.**

**DEPARTMENT OF PHYSIOLOGICAL SCIENCE
UNIVERSITY OF CALIFORNIA, LOS ANGELES
405 HILGARD AVENUE
LOS ANGELES, CALIFORNIA 90024-1527**

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STATEMENT OF PROGRESS

4/1/94 - 6/30/95

The following work related to this grant was completed during the period indicated above:

1. Electrical Stimulation of Peripheral Nerves - Effects on Growth Hormone (GH) Secretion

The following study was done in males earlier and was essentially repeated in females. Normal rats were anesthetized and prepared for one of the following procedures using the tibial (T), peroneal (P), sural (Su), and/or soleus (So) nerves:

- sham control - dissection of the nerves but no transection or stimulation
- nerve transection and stimulation of the proximal end of T, P and Su
- nerve transection and stimulation of the distal end of T, P and Su
- nerve transection and stimulation of proximal end of T and Su

Maximum stimulation (at a rate and duration mimicking that observed during treadmill stepping) was administered to the nerves via bipolar silver electrodes using a Grass stimulator for 15min. At the conclusion of the stimulation, a blood sample was taken by cardiac puncture and the rats were sacrificed immediately. The anterior pituitary gland and hypothalamus were removed as rapidly as possible. Pituitary and plasma bioactive and immunoactive GH were measured. Plasma T3, T4, corticosterone, testosterone, glucose, triglycerides and lactate levels were also determined.

Results: Stimulation of the proximal end of either the T, P and Su or T and Su resulted in a significant decrease in the pituitary and increase in the plasma bioactive GH levels. No change in any other parameter was observed. In contrast, no changes were observed when the distal end of the cut nerves were stimulated.

Significance: These data clearly demonstrate that sensory input from the periphery is an important source of control of GH secretion. These data are in agreement with the observation that GH secretion is inhibited during both spaceflight and hindlimb suspension and elevated during exercise. These data showed that the response was similar in male and female rats.

Two abstracts were presented on this data:

1. Grindeland, R.E., Roy, R.R., Edgerton, V.R., Gosselink, K.L., Grossman, E.J., and Sawchenko, P.E. Secretion of growth hormone in response to muscle sensory nerve stimulation. *Proc. 76th Ann. Meet. Endocrine Soc.*, 1994.

2. Gosselink, K.L., Grindeland, R.E., Roy, R.R., Edgerton, V.R., Grossman, E.J., and Sawchenko, P.E. Effects of hindlimb nerve stimulation on secretion of growth hormone in females. *ASGSB Bull.* 8:74, 1994.

In addition, a grant has been submitted to continue this work and is being reviewed at this time.

2. Rat Tendon Force Buckle Development

The development of the rat tendon force buckles has continued. Some EMG and force data from the plantaris muscle (a primary ankle extensor) have been collected while the rats were walking overground or on a treadmill, swimming or hindlimb suspended. Since the transducer has a very short life-span at this time, the data are minimal. We are continuing to test different bonding materials for the strain gauges and different substances for the buckle elements themselves. The preliminary results are encouraging: the plantaris forces and EMG appear to be consistent with that expected under these different loading conditions. During this period we wrote a NASA Grant in an attempt to secure funding for these studies. The Grant has been not funded at this time.

3. Rat Centrifuge Study

We completed our analyses of the soleus and medial gastrocnemius from rats that were centrifuged for 14 days at 2G.

Results: The absolute soleus muscle mass was maintained during the centrifugation period while the medial gastrocnemius was decreased. However, since the body weights were decreased significantly during the centrifugation, the soleus mass relative to body weight was actually increased while that of the medial gastrocnemius was maintained at control levels. Based on immunohistochemical and gel electrophoresis techniques, there were no major adaptations in the myosin heavy chain profiles of these muscles after centrifugation. In addition, fiber size was essentially maintained in the fibers of the soleus and some subtle indications of atrophy was present in the medial gastrocnemius fibers.

Significance: These data indicate that chronic centrifugation of normal rats at 2G for two weeks (the same time period that rats were flown in Cosmos 2044) results in a decrease in the body weights of the rats. Apparently, this stimulus results in the maintenance of the absolute mass of the slow soleus, but not the fast medial gastrocnemius. Thus it appears that there may be some benefit of chronic centrifugation in "loading" predominantly slow extensors. These initial results should stimulate further studies related to the potential of using centrifugation as a countermeasure of unloading-induced muscle atrophy, e.g., during spaceflight.

One abstract has been presented on this data:

Roy, R.R., Roy, M.E., Mendoza, R., Talmadge, R.J., Grindeland, R.E., Vasques, M., and Edgerton, V.R. Response of rat skeletal muscles to 14 days at 2G. *ASGSB Bull.* 8:94, 1994.

A manuscript is now being evaluated for publication in a special supplemental issue of *Aviation, Space and Environmental Medicine*.

4. Hindlimb Suspension of Hypophysectomized Rats

We have completed the analyses of the fiber size and type adaptations in ambulatory and hindlimb suspended, hypophysectomized rats that were treated with growth hormone (GH), insulin-like growth factor-I (IGF-I) and/or high resistive climbing exercise (3 short bouts/day) during a 10-day suspension period. Several studies have been performed and the analysis of the data from each study are at different stages. Some of the major preliminary findings are discussed below.

Preliminary Results: Muscles from hypophysectomized rats show a typical differential atrophic response of the hindlimb muscles, i.e., the extensors atrophy more than the flexors. GH or IGF-I alone somewhat ameliorate the atrophic response in the extensors, with GH having a stronger effect. Exercise alone has little effect. The combination of GH (and IGF-I to a lesser extent) and exercise treatment returns the muscle mass to new control levels. Using a battery of immunohistochemical monoclonal antibodies reacting against specific MHC isoforms, it appears the hypophysectomized rats have a high percentage of fibers expressing multiple forms of MHC isoforms, including some developmental isoforms not normally observed in intact adult rats. In the soleus of suspended rats, there is an increase in the number of fibers expressing fast sarcoplasmic reticulum ATPase and in those expressing both the slow and fast forms (dual expression) compared to control. In the MG of rats that were exercised, there is an increased amount of co-expression with embryonic MHCs. In general, however, it appears that the muscles from hypophysectomized rats are much more resistant to fiber type adaptations than those from normal, sedentary control rats. However, they do show a similar atrophic response as described above and thus serve as an excellent model for testing the effects of hormonal replacement therapy.

Several abstracts and one article related to these data have already been presented:

- Gosselink, K.L., Grindeland, R.E., Roy, R.R., Mukku, V.R., Talmadge, R.J., Edgerton, V.R., and Linderman, J.K. Effects of growth hormone and insulin-like growth factor-1 with and without exercise on hypophysectomized hindlimb suspended rats. *FASEB J.* 8:A10, 1994.
- Gosselink, K.L., Grindeland, R.E., Roy, R.R., Edgerton, V.R., Grossman, E.J., and Sawchenko, P.E. Effects of hindlimb nerve stimulation on secretion of growth hormone in females. *ASGSB Bull.* 8:74, 1994.
- Grindeland, R.E., Roy, R., Edgerton, V.R., Grossman, E., Rudolph, I., Pierotti, D. and Goldman, B. Exercise and growth hormone (GH) have synergistic effects on skeletal muscle and tibias of suspended rats. *FASEB J.* 5:A1071, 1991.
- Grindeland, R.E., Roy, R.R., Edgerton, V.R., Mukku, V.R., Grossman, E. and Talmadge, R. Effect of insulin-like growth factor-I (IGF-I) on skeletal muscles and the tibias of suspended rats. *Proc. 74th Ann. Meet. Endocrine Soc.:*A118, 1992.
- Grindeland, R.E., Roy, R.R., Edgerton, V.R., Grossman, E.J., Mukku, V.R., Jiang, B., Pierotti, D.J. and Rudolph, I. Interactive effects of growth hormone and exercise on muscle mass in suspended rats. *Am. J. Physiol.* 267:R316-R322, 1994.
- Grossman, E.J., Roy, R.R., Grindeland, R.E., Talmadge, R.J., and Edgerton, V.R. Hormone and exercise effects on the size and myosin heavy chain profiles of medial gastrocnemius fibers in hypophysectomized suspended rats. *ASGSB Bull.* 8:80, 1994.
- Roy, R.R., Grindeland, R.E., Grossman, E., Mukku, V., Talmadge, R. and Edgerton, V.R. Growth hormone, insulin-like growth factor-1 and exercise interactions in maintaining muscle mass during hindlimb suspension of hypophysectomized rats. *ASGSB Bull.* 6:94, 1992.

In addition, three manuscripts are now being finalized for submission for publication in the Journal of Applied Physiology or the American Journal of Physiology.